INVITED COMMENT

P values may lack power: The choice of conduit for above-knee femoropopliteal bypass graft

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Truth lies within a little and certain compass, but error is immense.

Henry St. John, Viscount Bolingbroke (*Reflections upon Exile*, 1716)

In January 1988, I was called to evaluate a 67-year-old man (Bob) with an acutely ischemic foot. The previous year he had undergone a left femoral to above-knee popliteal artery bypass graft with 6-mm polytetrafluoroethylene (PTFE) at another hospital. His claudication completely resolved until the sudden onset of a cool, pale, numb foot several hours before he went to the emergency department. I asked the patient if his vein had been inadequate. Bob replied that his initial surgeon stated that PTFE would be a good initial choice, saving the vein for later. After reviewing the options, I proceeded with a femoral to below-knee popliteal artery bypass graft with ipsilateral reversed saphenous vein; thrombectomy of the outflow arteries was required to extract propagated distal thrombus. While preparing this commentary, I received a Christmas card from Bob. I contacted him to learn that his vein graft, verified by duplex scan, remains patent 12 years later. His saphenous vein was never required for coronary bypass graft.

The article in this issue entitled "A prospective randomized trial comparing vein with polytetrafluoroethylene in above-knee femoropopliteal bypass grafts"[1] is an attempt to determine the better approach for a patient such as the one described above. In this era of evidence-based medicine, the *P* value has become the Holy Grail. The authors randomized 136 patients undergoing 151 primary above-knee femoropopliteal bypass grafts and present their 2-year results. The stated aims of the study were to answer three questions: (1) Is there a difference in cumulative patency rates between saphenous vein and PTFE bypass grafts? (2) What are the consequences of bypass graft failure? and (3) If PTFE was used, is the autologous vein still later available and usable for more distal procedures? Below, I review the authors' data and pertinent literature. Reluctantly, but of necessity, a brief foray into the realm of biomedical statistics is performed to evaluate the reliability of the authors' study design and conclusions.

IMPORTANT PECULIARITIES OF *P* VALUES: IS THERE A DIFFERENCE IN CUMULATIVE PATENCY RATES BETWEEN SAPHENOUS VEIN AND PTFE BYPASS GRAFTS?

For infrageniculate popliteal and tibial artery bypass grafts, vein has clearly been shown to be superior to prosthetic. The situation is less clear for above-knee bypass. Surprisingly, I could identify only two prospective randomized trials comparing vein versus PTFE that included above-knee femoropopliteal bypass. Neither study is directly comparable with the present study of Burger et al, but both provide useful data for consideration. Tilanus et al[2] prospectively randomized 49 patients requiring femoropopliteal bypass to vein or PTFE. The 5-year primary patency rates were 37% for PTFE versus 70% for saphenous vein ($P < .001$). Unfortunately, the study included patients undergoing below-knee (n = 34) and above-knee (n = 15) bypass grafts, and the size of the latter subsample was insufficient to allow subgroup analysis.

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The largest published study comparing saphenous vein with PTFE for infrainguinal bypass was reported by Veith et al[3] in 1986 and included 845 infrainguinal bypass grafts, 176 of which were to the above-knee popliteal artery. The indication for surgery was limb salvage in 87% of patients, and 15% had undergone previous bypass grafting. In contrast, in the report by Burger et al, all patients were undergoing their first infrainguinal bypass graft, and 79% were claudicants. Despite these important differences, the reported results (and lack of a significant *P* value) of each study are superficially in agreement, and if improperly interpreted, will lead the unwary reader to an "immense error." In Veith et al's series, the 4-year primary patency rates were 61% for vein and 38% for PTFE ($P > .25$, not significant). The critical surveyor of life tables will note that only 14 of the original 167 patients were available for follow-up at 4 years, too few to generate a meaningful estimate of graft patency. To my knowledge, no subsequent report with longer follow-up of these patients was ever published. This unfortunate situation has led many to conclude that PTFE and vein for above-knee bypass grafts are "no different." Burger et al inadvertently perpetuate this misconception with the early publication of their prospective trial: "After two years, the primary patency of the saphenous vein was 83%, and of PTFE 67% ($P = .065$). . . . The use of PTFE above the knee is a reasonable alternative for femoropopliteal bypass that is associated with acceptable short-term patency rates." The reasons why lack of a significant *P* value does not necessarily imply that the two treatments are no different are complex and deserve further explanation.

Life table presentation of data is currently the accepted standard for analysis of graft patency and mortality. However, as succinctly outlined by Underwood et al,[4] the potential abuses of life table analysis are substantial. For life table patency curves to have any real meaning, the follow-up will invariably need to be considerably longer than the time period of primary interest to ensure that sufficiently large numbers of patients are available at a specified point in time for analysis. Thus, there are two ways of increasing the span of time over which patency curves remain reliable. The first is to extend the duration of the study until a sufficient number of patients have been followed up for the specific period of interest. The second is to increase the sample size to an adequate level. The obvious question that needs to be asked when designing or analyzing a clinical trial is, *what constitutes an adequate sample size*?

The probability of detecting a specified difference in outcome between treatment groups, if such a difference is present, is termed the *power* of the study. This probability depends not only on a large sample size, but also on the magnitude of the expected treatment difference. The literature suggests an expected 5-year primary patency of a PTFE bypass graft to the above-knee popliteal artery of 50% to 55% (reported range, 38%-65%; the only two reports exceeding 60% considered only patients with claudication), in contrast to a likely 5-year primary patency of 70% to 75% for saphenous vein. Michaels[5] published a detailed review of the choice of graft material for above-knee popliteal bypass that included a mathematical model. He estimated that "assuming there is actually a 20% difference in 5-year patency, the number of grafts required at 5 years in order to have a 95 per cent chance of showing significance ($p < 0.05$) is about 160 in each of the two randomized groups."

In both Veith et al's study and Burger et al's study, the number of patients entered into the trial is only approximately half of the number of patients that would need to be available at 2, 3, or 5 years (pick one) to generate a 95% chance of detecting a 20% difference in patency. The absence of statistical significance is thus entirely predictable. Such a potential statistical error has been termed a Type II or beta error, or a false-negative conclusion. Small trials are especially prone to such errors, particularly if the sample size is inadequate and the power is low. In addition, if the event rate is low during the period of analysis, a small trial will generally fail to detect a substantial outcome difference. Peto et al[6] addressed this issue in a landmark paper on clinical trials. In discussing a hypothetical small clinical trial of two different cancer treatments, they stated "even the substantial differences are by no means so substantial that small trials can readily detect them; it might be, for example, that when 50% of the control patients are dead, only 33% of the patients receiving the new treatment would be expected to have died. A difference of this magnitude has over 95% chance of being detected in a trial in which hundreds of patients are randomized and about 250 of them die, but only a 25% chance of being detected in a small trial in which dozens of patients are randomized and about 25 of them die." This issue assuredly applies to the present study of Burger et al. Only 31 events (graft occlusions) occurred during the entire observation period, 10 in the vein graft group and 21 in the PTFE group. With such a low event rate, either significantly more patients will require randomization or much longer follow-up will be necessary to

be reasonably sure that as much as a 20% patency difference is not present. I am confident that if such a study of appropriate design and power is ever carried out, no doubt a daunting task, such a difference (with a significant *P* value) will result in favor of vein.

It is also worth emphasizing that further small, single-center, clinical trials are unlikely to help, and, in fact, will increase the likelihood not only of false-negative results, but also of Type I or alpha errors, that is, false-positive results. As trial size decreases, the ratio of false-positive conclusions to expected true positives increases.[7] Small clinical trials also render stratification and subgroup analysis less feasible. Burger et al report that "none of the risk factors described in other studies [diabetes, smoking, patent outflow arteries] have a negative influence on the patency of the PTFE bypass graft." The inability to detect these differences undoubtedly reflects the unreliability of subgroup analysis when the size of the subsample is too small.

WHAT ARE THE CONSEQUENCES OF BYPASS GRAFT FAILURE?

A critical issue for those who advocate PTFE first for above-knee bypass relates to the consequences of bypass failure. Twenty-one PTFE grafts occluded, compared with 10 saphenous vein grafts, using the authors' own data. In addition to the twofold occlusion rate, 13 patients required reoperation in the PTFE group compared with only five in the vein group, a nearly threefold difference. The authors conclude "even from this small group of patients that the use of saphenous vein does result in less occlusions and less reoperations." I would not quibble with their conclusion. How do the authors' data stack up against other reports of PTFE grafts? In the oft-quoted UCLA series, it is of interest to examine the outcome of the 132 patients who were originally operated on for claudication.[8] Good-risk claudicants are often considered the best candidates for preferential above-knee PTFE bypass graft. The PTFE grafts failed in 28 patients, 20 (15%) of whom "manifested limb-threatening ischemia as a result of failure of a bypass that was originally placed for claudication."[8] Experienced surgeons have also noted the frequency with which the outflow tract seems to suffer after initial placement of a proximal PTFE bypass graft. Veith et al presciently noted that "ASV and PTFE grafts to the popliteal artery failed with roughly equal frequency up to 18 months; thereafter the PTFE grafts failed more frequently. This suggests that PTFE grafts, at least in the femoropopliteal position, may be disadvantaged because they promote progression of distal atherosclerosis in some as yet unclarified way."[3] It has also been suggested that distal embolization from PTFE femoropopliteal grafts may compromise the outflow tract. One is forced to conclude that the initial placement of PTFE significantly increases the likelihood that repeat intervention will be required. Although repeat leg bypass graft almost never performs as well as primary leg bypass graft, I would grudgingly admit that repeat leg bypass graft with good quality vein outperforms primary leg bypass graft with PTFE.

IF PTFE WAS USED, IS THE AUTOLOGOUS VEIN LATER STILL AVAILABLE AND USABLE?

The PTFE-first proponents suggest that vein sparing is an important concept. The present study did succeed in definitively answering this question: "None of the patients needed the vein for coronary bypass graft procedures within the follow-up period." Among the 31 occluded bypass grafts in the series of 151 patients, the vein that was spared was only used on three occasions.

Other investigators have examined this issue and reached similar conclusions.[9,10] The argument for saving the vein for later is not very persuasive. In addition, the issue does not even arise for the patient's first bypass graft on the index leg because the contralateral limb would have saphenous vein available for use during subsequent coronary artery bypass or peripheral bypass grafting.

Are there other potential advantages of using PTFE first that have not been addressed? In most studies, including the present one, a significantly shorter operating time is documented for PTFE bypass graft; time in the operating room was reduced by 32 minutes ($P = .002$). However, no study has demonstrated significantly less major morbidity or mortality associated with this time savings.

CONCLUSIONS

A proper clinical trial requires enrollment of large numbers of patients with adequate follow-up to ensure that the power of the study is sufficient to detect a difference. Consider that more than 1600 patients were enrolled in the Asymptomatic Carotid Atherosclerosis Trial to detect a statistically significant 55% reduction in stroke risk. Although the absolute stroke risks for the medical and surgical groups were virtually identical in the earlier Veteran's Administration Asymptomatic Carotid Surgery Trial,

the latter study of approximately 400 patients failed to generate a significant *P* value, a manifest Type II statistical error. This fatal flaw likely affects both the 1986 Veith et al report as well as the current study from the Netherlands. As Herodotus wrote in his *Histories*: "This is the bitterest pain among men, to have knowledge but no power." Repeated publication of clinical trials lacking statistical power will hinder, rather than further, expansion of our clinical knowledge base.

With respect to PTFE versus vein for primary above-knee bypass graft, I am fairly certain there is at least a 20% 5-year patency advantage in favor of vein. Existing randomized trials are flawed because of the lack of power resulting in a Type II error. The vein is rarely needed later. Using PTFE first significantly increases the likelihood that reintervention will be required. An initial operating time that is 32 minutes shorter ($P = .002$) is insufficient justification for compromising long-term results, particularly in patients with claudication in whom life expectancy is longer. Use the vein first if it is available. Despite the lack of a *P* value, Bob and I are in firm agreement on this issue.

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Please see the related article by Burger et al on pages 278-83.